THE MOUTH COVID CONNECTION

The importance of the oral cavity for the coronavirus disease – part I

Shervin Molayem[1], Carla Cruvinel Pontes[2]

1- DDS, Periodontist, Private Practice, Los Angeles, California

2- DDS, Periodontist, MsC, PhD, Dental Research Consultant at Smile@Research, Cape Town, South Africa

Corresponding author

Shervin Molayem

smolayem@gmail.com

Abstract

The mouth plays a crucial role as an entry point to SARS-CoV-2, and the presence of ACE-2 receptors in the oral cavity suggests that it can harbor viruses in the early stages of infection. The new coronavirus has been identified in saliva and its viral load has been linked to the severity of COVID-19. Direct and indirect transmission through oral fluid droplets plays a pivotal role in the spread of the disease. Saliva also plays a protective role against viruses and it is likely to become the new gold standard for COVID-19 testing. Hyposalivation can increase the risk for respiratory infections and COVID-19. Oral lesions are rare in COVID-19 patients, with reports of sialadenitis, mucositis, geographic tongue, burning mouth, necrotizing gingivitis and viral enanthema. Transient loss of taste and smell are highly prevalent symptoms, likely related to neurological changes. Due to the importance of the oral cavity and saliva in the development and transmission of the coronavirus disease, as healthcare professionals, dentists have a crucial role to play during the pandemic.

Key words: mouth covid, saliva covid, oral health covid, oral inflammation

Introduction

As the coronavirus disease pandemic unfolds, healthcare providers are expected to keep their knowledge on the disease and related protocols up to date, so they can better play their part in this unique global health crisis. The COVID-19 pandemic is caused by the novel SARS-CoV-2, a beta coronavirus closely related to SARS-CoV, which resulted in the occurrence of acute respiratory syndrome (SARS) in over 30 different countries in 2002. Five other coronaviruses have been found in humans, including -229E, HCoV-OC43, HKU1, HCoV-NL63, and the Middle East Respiratory Syndrome (MERS)-CoV. Coronaviruses constitute enveloped single-stranded RNA viruses that rely on the receptor angiotensin-converting enzyme 2 (ACE2) to infect human cells.[1]

During the pandemic, dentists are being called to the important task of reducing infection and inflammation in the mouth, particularly in the form of periodontal disease, while adhering to severe infection control measures to avoid the spread of COVID-19 between patients and staff.[2] Since up to 75% of infected individuals can be asymptomatic, in dental practices, all patients must be treated with extensive precautions.[3]

The identification of SARS-CoV-2 in saliva droplets of infected patients has shed light on the high risk of transmission through saliva, placing the oral cavity in a pivotal position as an entry point for the virus, together with the nasal cavity and the ocular mucosa.[4] Saliva can be used as a diagnostic tool for the identification of SARS-CoV-2, which points to the potential for the oral cavity to become a target for preventive interventions during the early stages of infection.[5]

The present review aims at exploring the role of the oral cavity in COVID-19 as well as its implications for dental practitioners and patients, including viral presence in the oral cavity, saliva's role, diagnosis of COVID-19, and alterations in the oral cavity of COVID-19 patients.

Oral cavity as a portal to COVID-19 infection

The oral cavity provides an adequate niche for colonization and growth of microorganisms, presenting the second most diverse microbiota in the body after the gut. The oral microbiome is composed of over 700 species of microorganisms, including bacteria, viruses, fungi, and protozoa. While culture studies provided a limited approach to explore the microbiome, genomic technologies have greatly increased our understanding of the highly complex oral environment.[6]

Adequate conditions in the oral cavity that favor microorganisms include stable temperature (37º C), salivary pH 6.5-7, and the presence of different niches, from hard dental tissues to soft mucosa.[7] Despite the favorable conditions, studies suggest that most viruses do not replicate in the oral cavity, but they replicate in the respiratory system and the gut. However, a few viruses, such as herpes and papillomaviruses, proliferate in oral epithelial cells and release viral particles to saliva, increasing the risk for development of mucosal lesions.[8]

COVID-19 receptors in the oral cavity

Infection by SARS-CoV-2 starts after the virus binds to host cells through ACE-2 receptors, which mediate viral entry. In an in vitro study, Xu et al. (2020) confirmed the expression of ACE-2 in the oral mucosa, with the highest expression in epithelial cells from the tongue and salivary glands.[9,10] ACE-2 receptors are expressed in a variety of

human cells, including alveolar epithelial cells, pneumocytes, and vascular epithelium, and expression increases with aging.[11] High ACE-2 expression has been linked to increased susceptibility to COVID-19 infection, thus the oral cavity plays a crucial role in the viral infection.[11] In addition to the ACE-2 receptor, furin has also been linked to viral invasion of host cells. Furin is a host protease suggested to facilitate cleavage of SARS-CoV-2 glycoproteins on the viral envelope and infection. In the oral cavity, furin is mostly expressed on the tongue and in mucosal epithelial cells.[12,13]

SARS-CoV2 in the oral cavity

In vitro studies on SARS-CoV indicate that it takes about 10 minutes for the virus to enter a host cell, and 10 hours for the host cell to produce and release virions (viral particles) to the extracellular environment. One single infected cell can produce approximately 10^3 virions, which is also known as the per-cell viral yield.[14] In the transmission of SARS-CoV-2, the oral cavity, nasal cavity, and eyes constitute entry points to viral particles from the environment and/or from other infected hosts.[15] Besides direct exposure to the virus, Sabino-Silva et al. suggest three indirect mechanisms to explain the presence of SARS-CoV2 in the oral cavity:[4]

(1) Viruses in the respiratory tract can reach the oral cavity through droplets of respiratory mucous, which are often exchanged between the mouth and respiratory tract through coughing and sneezing.

(2) Viruses in the systemic circulation can reach the oral cavity through the gingival crevicular fluid.

(3) Minor and major salivary glands can harbor the virus and release infective particles to saliva through salivary ducts.

Studies have confirmed the presence of SARS-CoV-2 in saliva samples from COVID-19 patients.[16–20], with 25% of patients from one study showing live viruses.[16] However, the behavior of the virus in the oral cavity is unknown, with factors such as the composition of the oral microbiota, the composition and production of saliva, and oral diseases potentially influencing the virus' ability to infect oral cells.[21]

Based on findings from previous studies, it can be suggested that once in the oral cavity, SARS-Cov-2 can:

- Interact with the oral microbiome.[22]
- Invade oral cells and replicate, with the potential to cause local lesions.[21]
- Invade and replicate in minor salivary glands, forming a reservoir for infection.[9]
- Get access to the respiratory tract through aspiration.[23]
- Get swallowed and lead to local changes in the gut, resulting in digestive symptoms such as diarrhea, vomiting, or abdominal pain.[24]

The role of saliva in COVID-19 infection

Transmission routes for SARS-Cov-2

The most common transmission routes for SARS-CoV-2 include contact and direct transmission. Direct transmission includes exposure to the virus through coughing, sneezing, and/or inhalation of droplets from infected individuals, which contain a mixture of saliva and respiratory mucous. Indirect transmission occurs when the oral, nasal, or ocular mucosa gets in contact with contaminated hands, objects, or surfaces. Transmission through aerosols and the fecal-oral route are also thought to contribute to the spread of COVID-19.[25,26]

Viral load in saliva

In 2004, a study on the first coronavirus outbreak (SARS-CoV) suggested that transmission occurred mainly through droplets from the oral cavity or respiratory tract during conversation, coughing, or sneezing, indicating the importance of saliva droplets. The authors reported high amounts of virus RNA in saliva (7.08×10^3 to 6.38×10^8 copies/mL) and throat wash (9.58×10^2 to 5.93×10^6 copies/mL) of SARS patients.[27]

A recent study on SARS-CoV-2 showed a high salivary viral load in samples from the posterior throat of COVID-19 patients (10^4 – 10^6 copies/mL). The highest viral load was observed up to a week after onset of symptoms and, despite the decline with time, in 40% of the evaluated patients, viral RNA was still detected after 14 days.[28] The elevated salivary viral load can be linked to the high person-to-person transmissibility.

Yoon et al. evaluated the viral load in two hospitalized COVID-19 patients in saliva, sputum, nasopharynx, oropharynx, and urine. Saliva presented a consistently high viral load, which was higher than the oropharynx in the early stages of the disease.[29]

One of the biggest challenges regarding the transmission of COVID-19 relates to the spread of droplets. It has been estimated that sneezing spreads around 40.000 droplet nuclei, coughing spreads around 3.000, and talking generates 600 droplet nuclei per minute. While saliva droplets over 60µm in diameter tend to settle quickly on surfaces, smaller droplets are likely to be involved in inter-individual transmission. Droplets with diameter >10 µm tend to evaporate and turn into droplet nuclei, potentially contributing to aerosol transmission. [30–32] Studies on SARS coronaviruses report that droplets can persist for 4 hours in copper, 24 hours on cardboard, and at least 4 days in wood, glass, and plastic surfaces, which highlights the importance of strict infection control measures.[33]

COVID-19 and the risk for aerosol transmission

The importance of aerosols for the transmission of COVID-19 has been discussed. Aerosols consist of small particles ranging from 0.001 to >100 μm, which remain suspended in the air. The World Health Organization (WHO) has suggested that aerosol-generating dental procedures can lead to the spreading of SARS-CoV2, one of the reasons why they recommend postponing elective dental procedures.

In order for aerosols to be infective, three main factors need to be considered: the time that saliva droplets remain in the air (physical decay), the time that the virus remains infectious (biological decay), and the acquisition of droplets by a susceptible host.[34] A study from China tested 35 aerosol samples from two hospitals in Wuhan and the results showed low to undetectable SARS-CoV-2 RNA in samples from patient areas and positive samples from floor surfaces (deposition aerosol), suggesting that droplets in the air are not a problem; however, infection control measures are crucial for floor and surfaces.[35]

Dental-generated aerosols typically result from water and air spray, with the potential to markedly dilute viruses. Furthermore, high-volume evacuation systems used in dental clinics reduce aerosol significantly.[36] Lastly, dental professionals have routinely used personal protective equipment (PPE) due to the possibility of transmission of HIV, hepatitis, and other contagious diseases. High standards of infection control have been the norm in daily dental practice.

It has been suggested that oral rinsing before dental procedures can reduce the viral load. In a meta-analysis from Marui et al. (2019), chlorhexidine, essential oils, and cetylpyridinium chloride mouthwashes reduced the number of disseminated microorganisms by 64.8% when used before dental procedures.[37] To the best of our knowledge, there is currently no evidence that SARS-CoV-2 remains viable and

infective in dental aerosols, and no data on the transmission through dental practices is available.

Salivary glands and SARS-CoV2

In an experimental study on SARS-CoV in rhesus macaques, epithelial cells from salivary glands expressed ACE-2 and became infected.[38] Findings from another SARS-CoV study showed that viral RNA was detected in saliva before the development of lung infection.[27]

In an *in vitro* study of human tissues, Xu et al. reported mean expression of ACE-2 in salivary glands of 1.8 pTPM (protein-coding transcripts per million), which is the 10th highest expression in the body, higher than in pulmonary tissues.[9] Liu et al. (2020) reported a high expression of ACE-2 receptors on epithelial cells of salivary ducts.[38] Together, these findings suggest that salivary glands can be initial targets for COVID-19 infection, being able to function as a reservoir for the virus, particularly in asymptomatic patients.[9]

Hyposalivation can be a risk factor for COVID-19

A series of proteins present in human saliva has demonstrated anti-viral activity, such as mucins, cathelicidin, lysozyme, peroxidase, agglutinin, cystatins, lactoferrin, alpha, and beta-defensins.[6] Although the anti-viral role of saliva against SARS-CoV2 has not been explored, it can be speculated that invasion of oral cells is a challenging viral task. Thus, hyposalivation, which describes a decrease in saliva flow, is likely to increase the risk for respiratory infection in COVID-19 patients.[39] A prospective study from Iwabuchi et al. reported a higher incidence of acute respiratory infections in subjects with hyposalivation, with an odds ratio of 1.76, meaning that a patient with hyposalivation has nearly 1.8 more chance of developing respiratory infections. The authors suggested

that hyposalivation can lead to impaired protection of the oral and respiratory mucosa, and to a higher risk for viral adhesion and replication.[40]

Criteria for diagnosis of hyposalivation:[41]

Stimulated salivary flow rate = ≤0.5–0.7 mL/min

Unstimulated salivary flow rate = ≤0.1 mL/min

Hyposalivation often manifests as xerostomia, particularly in the elderly. The etiological factors for hyposalivation include autoimmune, endocrine, neurologic, and infectious diseases, use of medications (antidepressants, antipsychotics, and antihistamine drugs), and radiotherapy for head and neck cancer. Treatment strategies for hyposalivation are mostly palliative, including saliva substitutes, salivary stimulants, topical agents, and systemic sialogogues.[42]

SARS-CoV2 salivary diagnosis

Diagnostic tests

COVID-19 tests to detect current infection are based on nucleic acid amplification to identify viral RNA, typically through Polymerase Chain reaction (PCR). For diagnosis, samples are collected from the nasopharynx, oropharynx, or sputum using a swab, which is transferred to a liquid, where viral RNA is released, extracted, and amplified.[43] Nasopharyngeal swabs collected by healthcare professionals are the gold standard for diagnostic testing of SARS-CoV-2 due to their high sensitivity and specificity. Nonetheless, they are invasive, can cause discomfort, and if handled incorrectly, it can lead to coughing, bleeding, and lower test accuracy. [28]

Saliva tests present the advantages of being non-invasive, convenient due to large supply and painless nature of the test, presenting easy collection, with potential for self-collection (Figure 1). Salivary tests are safe, present lower risk for operator error, and can be performed in most patients, including children, the elderly and the disabled. In the diagnosis of respiratory viruses in hospitalized patients, a high correlation between nasopharyngeal fluids and saliva has been reported.[44] Few studies have evaluated different methods for saliva collection, including swab, coughed out or spit out saliva, and collection from salivary gland ducts. The limitations of salivary diagnosis for COVID-19 include the limited number of studies, the influence of the collection method, and salivary changes on test results.

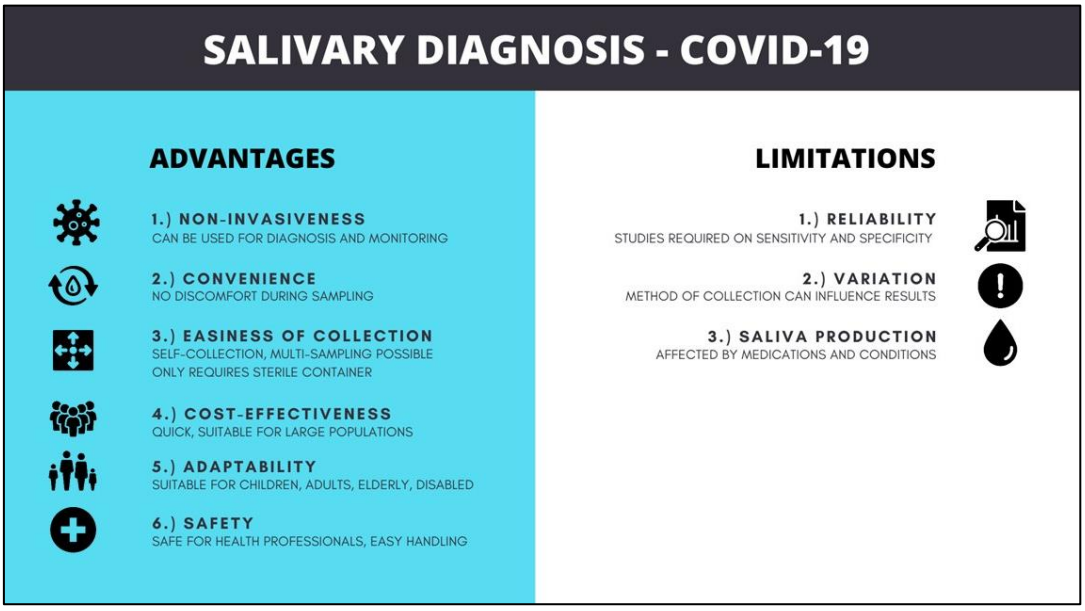

Figure 1. Advantages and limitations of salivary testing to diagnose COVID-19 infection.

Saliva swabs

In a study by Zhang et al. (2020), saliva swabs were positive in only 50% of confirmed COVID-19 patients.[19] In another study that used the saliva drooling technique, all samples (n=25) tested positive, and the authors concluded that saliva was a reliable diagnostic tool.[45]

Coughed out or spit out saliva

Deep throat saliva can have higher diagnostic value, as suggested by results from two studies from the same group. In one study, positive results were present in 91.7% of positive patients, and in the second study, virus RNA was detected in 86.9% of saliva samples.[16,28] Yoon et al. (2020) reported a remarkably high viral load of SARS-CoV-2 in the saliva of two hospitalized patients, who were instructed to self-collect saliva by spitting out into collection tubes.[29]

In a more recent study that included 1,104 samples from 386 patients, self-collected spit-out saliva was as effective as nasopharyngeal swabs collected by healthcare professionals. Interestingly, saliva presented higher reliability than anterior nasal swab in the study.[46]

Salivary gland duct

Chen et al. (2020) collected saliva from a salivary gland duct and reported that only 12.9% of confirmed COVID-19 cases tested positive. Because three of the four patients who tested positive for salivary gland saliva were on ventilators, the authors suggested that this method can indicate the severity of the disease.[20]

Further confirmation on salivary diagnosis comes from the study of Wyllie et al. (2020). Using PCR tests, higher viral RNA was found in saliva as compared to nasopharynx swabs in 70 hospitalized COVID-19 patients. Furthermore, 1-5 days after the initial diagnosis, 71% of the nasopharynx samples and 81% of salivary samples remained

positive, suggesting that saliva is as least as sensitive as nasopharyngeal swabs to detect SARS-CoV-2.[47] Thus, the diagnostic value of saliva for COVID-19 is increasing rapidly. It can become the new gold standard in the near future, as more studies are reporting its comparability to nasopharyngeal samples.

Antibody tests

In addition to genetic tests, serological tests have been used to detect anti-SARS-CoV-2 antibodies, including IgM, IgG, and IgA. However, serological tests are more suitable to evaluate the host response and identify previous infection, while genetic tests are the best option to identify current infection.[48]

Saliva has the potential to not only provide a diagnosis for COVID-19, but also for monitoring viral loading during disease, At this point, there are no studies investigating salivary antibodies against SARS-CoV-2.[12]

New salivary tests for COVID-19

A new quick test to detect SARS-CoV-2 in saliva through simplified PCR has been developed by the Yale School of Public Health, and its use has recently been authorized by the U.S. Food and Drug Administration (FDA).[49] A spectroscopy-based portable diagnostic test that relies on artificial intelligence has been developed and pre-clinically evaluated for dengue and Chikungunya Virus with promising results (99% success). It can be used with serum or saliva samples for diagnosis and estimation of viral load.[50] Another diagnostic development comes from Virginia Tech, where engineering professors have created a test to detect the virus in droplets through biosensing. This nanotechnology combined with laser beams will be able to give results within minutes.[51]

While most current diagnostic tests rely on PCR, new antigen tests are being developed, since SARS-CoV-2 present multiple surface proteins that function as antigens.[52] Antigen tests can decrease time and cost, however, their reliability seems to be lower than PCR based-tests. Different laboratories have antigen tests in the market, however, recent studies suggest the low sensitivity (30.2% in one study and 11.1-45.7% in another study) is not adequate for the diagnosis of COVID-19.[52,53]

In a recent comprehensive review, findings from 28 studies that evaluated the presence of SARS-CoV-2 in saliva samples were summarized. In saliva, the viral load ranged from 9.9 × 102 to 1.2 × 108 copies/mL. When compared to the gold standard, the sensitivity of saliva tests ranged 66-91.7% and specificity ranged 97-100%, with saliva presenting considerably lower costs. Factors that are likely to affect salivary results include time for collection during the day, collection method, and stage of the disease.[54]

Oral findings in COVID-19 patients

Gustatory dysfunction

Loss of taste (ageusia) has been strongly linked to COVID-19, being often associated with total or partial loss of smell (anosmia or hyposmia, respectively). In a multicenter study, over 80% of COVID-19 patients with mild to moderate symptoms had olfactory and/or gustatory dysfunction.[55] A meta-analysis from Tong et al. (2020) reported prevalence of olfactory dysfunction (anosmia) of 52.7% (range 5.61% to 92.65%) and gustatory dysfunction of 43.9% (5.61% to 92.65%) in COVID-19 patients. The authors highlighted the well-established link between olfactory function and taste, hence it is not clear whether gustatory dysfunction is an independent condition or a consequence of olfactory dysfunction, with 10.2 to 22.5% of patients presenting gustatory dysfunction

alone.[55–58] In 35.5% of the patients included in the study from Beltrán-Corbellini et al., olfactory or gustatory dysfunction was the first clinical symptoms of COVID-19.[59]

Anosmia and hypogeusia can be present in the absence of other symptoms and typically develop during the initial phase of the coronavirus disease.[60] The pathophysiology of gustatory and olfactory alterations related to SARS-CoV-2 is not fully understood. Because these symptoms can be present in the absence of inflammation, they are most likely linked to neurological alterations and damage to receptors.[61] Taken together, these findings indicate that olfactory and/or gustatory dysfunction can be diagnostic markers that suggest the need for diagnostic testing and self-isolation.[56]

Salivary gland conditions

In the literature, acute parotitis and submandibular sialadenitis have been reported in two COVID-19 patients. Both patients had systemic comorbidities and presented pre-auricular swelling, with one patient also presenting submandibular swelling.[62] In another report, acute parotitis was diagnosed in an otherwise healthy COVID-19 patient.[63] In both case reports, the alterations disappeared after resolution of the viral infection. Despite the infrequency of salivary glands changes, dentists and physicians should be aware of this potential manifestation of COVID-19.

Oral mucosal lesions

With the increase in studies reporting COVID-19-related cutaneous conditions, known as viral exanthem or skin rashes, the mouth has received more attention during clinical examination. In the oral cavity, viral lesions can be present in the form of viral enanthem, typically manifesting as vesicular, macular, papular, and/or petechial lesions. A few case reports present oral lesions in COVID-19 patients, with most resembling viral enanthem (Table 1). Viral enanthem has been reported for Dengue, Chikungunya,

Ebola, Herpes, HIV, Epstein–Barr, Varicella-zoster, and Paramyxoviridae viruses.[64] According to Jimenes-Cauhe et al. (2020), 29% of COVID-19 patients presenting exanthem also presented enanthem, with petechiae in the palate being the most common clinical presentation.[65]

In a case report from France, a COVID-19 patient presented an irregular ulcer on the tongue dorsum that started as a painful papillae inflammation and erythema, and the lesion disappeared after 3 days.[66] In another report from Spain, one confirmed patient and two patients suspected to be infected presented minor palatal ulcers, small blisters in the vermillion border, and generalized desquamative gingivitis.[67] Ulcers in the gingiva, palate and tongue were also described in one case report from Italy[68] and two patients from Iran.[69] An erythematous palatal lesion that extended to the oropharynx was report in a Turkish COVID-19 patient.[70]

In a case report from Brazil, a COVID-19 patient who had other systemic conditions presented a macular white plaque on the tongue dorsum, diagnosed as a fungal infection, and small ulcers in the oral mucosa.[71] Soares et al. (2020) reported oral lesions in another COVID-19 patient from Brazil who was admitted to hospital, in the form of a red diffuse lesion in the hard palate, an ischemic ulcer in the buccal mucosa, as well as multiple macules in the tongue, palate, and lips.[72] Three patients that developed cutaneous erythema multiform–like lesions related to COVID-19 presented palatal macules and petechiae, according to a short correspondence article from Spain.[73] In one single case report from England, a COVID-19 patient developed necrotizing gingivitis.[74]

Currently, it is not clear if oral lesions in COVID-19 patients are a primary or secondary consequence of the viral infection.[65] The role of previous systemic conditions, the host

immune reaction and the use of medications have been suggested as contributing factors in the development of oral lesions in those patients. Oral lesions are rare in COVID-19 patients, and the current evidence is not strong enough to suggest viral damage to oral cells. The lesions described so far probably result from drug-related reactions, opportunistic infections, and/or hypersensitivity.[75]

Take-home message

Oral cavity, infection and transmission. The oral cavity is an important entry point to the body, and its unique environment is favorable for microorganisms. ACE-2 receptors are expressed in the oral mucosa, particularly in salivary glands, suggesting that they can harbor viruses in the early stages of infection. Direct and indirect transmission through oral fluid droplets plays a pivotal role in the spread of the disease.

Viral behavior in the oral cavity. Once in the mouth, the virus can potentially interact with the microbiome, invade oral cells and salivary glands, and reach other organs, such as lungs and intestines, through aspiration and swallowing, respectively.

Viral load. SARS-Cov-2 has been identified in high levels in the oral cavity, and salivary viral load has been linked to the severity of COVID-19 infection.

Saliva's role. Saliva can be a culprit when it comes to transmission, but it also presents anti-viral properties. Hyposalivation can increase the risk for COVID-19 due to impaired protection of the mucosa. Dentists should be aware of the diagnostic criteria for hyposalivation and offer adequate treatment approaches when necessary.

Diagnosis. For the diagnosis of COVID-19, saliva is likely to become the new gold standard, presenting comparable results to nasopharyngeal swabs. New diagnostic

salivary approaches are being developed for quicker and more affordable tests, which will be a game-changer for health professionals.

Oral lesions. Oral lesions are rare in COVID-19 patients, with reports of sialadenitis, mucositis, geographic tongue, burning mouth, and viral enanthema that can manifest as petechiae, macules, papules, or ulcers. Transient loss of taste and smell are highly prevalent.

Despite the ethical challenges that might limit the conduction of studies during the pandemic, it is imperative to highlight the need for high-level evidence research to help elucidate the possible connection between COVID-19 and the oral cavity.

Conclusion

The oral cavity is a crucial entry point for microorganisms. SARS-Cov-2 has been identified in high levels in the oral cavity, and salivary viral load has been linked to the severity of COVID-19 infection. Saliva plays a pivotal role in infection and transmission, with hyposalivation potentially increasing the risk for COVID-19 due to impaired mucosal protection. Due to the multiple advantages of salivary tests, they are likely to become the new gold standard for COVID-19 diagnosis. While oral mucosal lesions are rare in COVID-19 patients and possibly develop as a secondary reaction to the virus, loss of taste and smell are a frequent symptom. Due to the importance of the oral cavity and saliva in the development and transmission of the coronavirus disease, dentists have a crucial role to play as healthcare professionals during the pandemic.

Study	Country	Age	Gender	Health conditions	Oral lesions					Skin lesions
					Features	Onset	Management	Duration	Tentative diagnosis	
Carrera-Presas et al. [67]	Spain	65	Female	Obesity, hypertension	Blisters in lower lip mucosa, desquamative gingivitis	With initial general symptoms	Topical mouthwash, systemic prednisone 30 mg/day	3 days	Viral enanthema	Rash under breasts, back, and genital area
		56	Male	No	Ulcers in hard palate (similar to herpetic ulcers)	2 days after fever onset	Valaciclovir 500 mg every 8 h, chlorhexidine and hyaluronic acid mouthwash for 10 days	10 days	Recurrent herpetic stomatitis	No
		58	Male	Diabetes, hypertension	Herpetic-like ulcers in left palate	Not clear	Topical antiseptic mouthwash	1 week	Recurrent herpetic stomatitis	No
Soares et al. [72]	Brazil	42	Male	Diabetes, hypertension	Ischemic ulcer in buccal mucosa, multiple red macules in hard palate, tongue, and lips	Not clear	Follow-up	3 weeks	Viral enanthema	Petechia, small vesicobullous lesions
Ciccarese et al.[68]	Italy	19	Female	No	Ulcers, erosions on inner lip, petechiae on palate and gingiva	5 days after general symptoms	Palliative	5 days	Petechiae	Erythematous macules, papules, and petechiae on lower extremities
Ansari et al.[69]	Iran	56	Female	Diabetes	Painful ulcers with irregular margins in hard palate	5 days after general symptoms	Topical diphenhydramine, dexamethasone, tetracycline, lidocaine	1 week	Opportunistic bacterial infection	No
		75	Male	Hypertension	Small ulcers, with irregular margins, in anterior tongue	1 week after hospital admission	Topical diphenhydramine, dexamethasone, tetracycline, and lidocaine	1 week	Opportunistic bacterial infection	No
Santos et al.[71]	Brazil	67	Male	Coronary heart disease, kidney transplant	White plaque, multiple ulcers in tongue dorsum	24 days after hospital admission	Fluconazole, nystatin, chlorhexidine digluconate (0.12%), topical daily 1% hydrogen peroxide.	2 weeks	Fungal infection (tongue scrap culture)	No
Kahraman & Çaşkurlu[70]	Turkey	51	Male	No	Erythematous lesion in oropharynx and hard palate, petechiae and pustular enanthema near soft palate	With general symptoms	Antibiotics	Unclear	Oral mucositis	No
Chaux-Bodard et al.[66]	France	45	Female	No	Irregular ulcer in dorsum of tongue	8 days after initial general symptoms	Follow-up	10 days	Viral enanthema	Erythematous lesion on big toe
Patel & Wooley[74]	England	35	Female	No	Erythematous, edematous gingiva, necrotic papillae	3 days after fever onset	400 mg metronidazole 3x daily for 5 days, 0.12% chlorhexidine for 10 days	5 days	Necrotizing gingivitis	No

Tomo et al.[75]	Brazil	37	Female	No	Diffuse bilateral erythema, depapillated tongue borders	9 days after initial general symptoms	Chlorhexidine 0.12%	2 weeks	Oral mucositis	No
Jimenes-Cauhe et al.[65]	Spain	58-77	3 Females	Unclear	Palatal macules and petechiae	Unclear	Systemic corticosteroids	2-3 weeks	Unclear	Erythema multiform-like lesions

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